Fundamentals of Cancer Pain Management

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7.1 The Problem

Pain is the most common and most feared symptom among cancer patients. At least 75 % of cancer patients will have significant pain, and the pain usually increases as the disease progresses and the end of life nears. While fatigue may be more common, and delirium and dyspnea near the end of life may be more bothersome to caregivers [1], pain is a common denominator in all of our conversations with cancer patients and their families. A meta-analysis of the prevalence of pain in cancer patients calculated rates of 33 % in patients after curative treatment, 59 % in patients undergoing cancer treatment, 64 % in patients with advanced/metastatic/terminal cancer, and an overall rate of 53 % [2].

One would think that in the developed world, after 50 years of opioid availability, 30 years of Continuing Medical Education (CME) about pain for healthcare practitioners, and 10 years of promulgation of "Pain as the 5th Vital Sign," that pain would be a solved problem. But it is not. Fisch and colleagues followed 3, 123 ambulatory cancer patients (breast, prostate, colon/rectum, lung) and found that 67 % had pain at their initial visit and 33 % were receiving inadequate analgesics.

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This inadequate analgesic prescribing persisted at follow-up visits and did not improve. Worse, minority patients had double the odds of inadequate prescribing [3]. Surprisingly, the figures have not changed appreciably from 18 years prior [4], even in a prospective study with interested participants who knew they were under observation.

While this situation is bad in the developed world [5], it is even worse in developing economies. Cancer is quickly becoming as common in the rest of the world [6] as in the developed – mostly Western – world. As life expectancy increases, and with adoption of the Western diet, cigarettes, industrialization, and the spread of cancer-causing viruses like Hepatitis C, cancer promises to be a leading global health problem far into the future: the World Health Organization estimates that annual cancer incidence will rise from 14 million in 2012 to 22 million within the next two decades [7].

The pain associated with these illnesses, magnified by the lack of opioid availability in many parts of the world, will grow as well. The World Health Organization (WHO) estimates that 80 % of the world's population does not have access to morphine for pain relief [8].

Curing cancer is often a necessary, but rarely a sufficient, step to relieve patients of their pain, because in addition to pain caused by the tumor, for many, pain arising from the treatment itself (radiation, chemotherapy, surgery) is significant and must be also addressed [9]. In an editorial in *the Journal of Clinical Oncology*, Martin Stockler called for "ensuring that every consultation includes the patient's rating of pain, that the oncologist pays attention to the answer, and that there is an agreed-upon plan to increase analgesia when it is inadequate" [10].

Universal adherence to this exhortation would certainly be helpful as far as it goes. The management of pain in cancer, even for the experienced clinician, is more nuanced and complicated than it may initially appear. Practitioners need to have a workable taxonomy of pain so that the therapies can be tailored appropriately. For example, "incident pain," which occurs when a limb is moved, requires a different approach than neuropathic pain occurring in the same location or visceral pain that may be present at the same time in another location.

To further complicate matters, it must be recognized that there are many variables that contribute to a pain symptom and, hence, more than one approach to treating pain is often needed. Dame Cicely Saunders pioneered the "Total Pain" concept that chronic pain arises from multiple dimensions of human experience – social, practical, spiritual, psychological, and physical [11]. This paradigm underpins the contemporary hospice and palliative care approach to pain and is the reason that palliative practice adopts a multidisciplinary approach to symptom management that can attend to any and all elements of a patient's suffering. It is important to remember, therefore, that when faced with difficult cancer pain, the primary provider and the patient will benefit by seeking help from a range of disciplines including, but not limited to, pastoral care and psychology. Even the best care utilizing the most advanced techniques and following the most current and evidence-based guidelines fails to deliver adequate pain relief to 10–20 % of patients [12].

7.2 Evidence

The International Society for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [13]. Acute pain is generally adaptive in that it causes avoidance of injurious situations or promotes healing by fostering immobilization of an injured body part. Chronic pain of the type associated with cancer does not have such adaptive purposes.

7.2.1 Pathophysiology of Pain in Cancer

The sensation of pain has been described as the result of a process "tantamount to an orchestral concert, with each individual instrument contributing a subtle yet important element composing the final product" [14]. Although considerable progress has been made in identifying the various elements involved in cancer pain and in understanding the complex process by which they interact, this field remains one in which novel discoveries have the potential to significantly contribute to mitigation of human suffering.

Pain in cancer is the result of complex interactions between cancer cells themselves, the peripheral and central nervous systems, and the immune system [15].

In this process, cancer cells produce a wide range of substances that mediate or interact with pain receptors (nociceptors). As more is understood about the functioning of these molecules in the transduction process, they have emerged as important targets for novel analgesic interventions [16]. Additionally, peripheral nocireceptors themselves appear to become activated, sensitized, or injured in the presence of certain cancers [17].

Once receptors are stimulated, impulses are transmitted first by afferent A-δ (thinly myelinated) fibers and later by slower (nonmyelinated) C-fibers. These end in cell bodies in the dorsal root or trigeminal ganglion that, in turn and in complex ways, interact with neurons in the central nervous system through cells in the spinal cord. These spinal cells project axons to the contralateral thalamus from which impulses are transmitted to regions of the cortex via somatosensory pathways. Interactions at the cortical level are highly complex involving the somatosensory cortex, frontal cortex, and limbic system.

The observation that perceptions of pain can vary depending upon factors that have no direct relation to nociceptors (anxiety, depression, distraction, etc.) indicates the presence of additional mechanisms that modulate transduction. These include inhibition at the spinal level by non-painful input (the Gate Theory), as well as descending inhibition from midbrain and higher regions that contain high concentrations of opioid receptors.

Visceral pain arising from nociceptors in internal organs is mostly transmitted by unmyelinated C-fibers. Often less well localized and less sharp than somatic pain, visceral pain is triggered by direct irritation from the tumor, distention or contraction of an organ, ischemia, necrosis, or inflammatory mediators.

Neuropathic pain arises from injury to nerve tissue in either the central or peripheral system. It differs from nociceptive pain in two important ways. First, there is no transduction from a nociceptor to a nerve. Rather, the nerve itself generates the pain impulse. Second, nerve damage is more likely than damage to other tissue to result in chronic pain; that is, the pain impulse continues after the insult is gone. The prognosis is, therefore, worse and such pain is less likely to respond to standard opioid or NSAID-based therapy [18]. Neuropathic pain is also complicated by the widely accepted "wind-up" phenomena: repetitive stimulation of the C-fibers leads to biochemical and physical genetic changes in the central nervous system. In fact, the damaged nerves and their undamaged counterparts may both be giving signals of the damaged nerves by crosstalk, reinforcing the pain stimulus [19].

In cancer, such injury often arises as a result of treatment (chemotherapy, surgery, or radiotherapy) but can also be caused by infection, direct action of the tumor, ischemia, or other mechanisms. Unlike somatic or visceral pain, the quality of neuropathic pain is often described as burning or numbing and may be further diagnosed as allodynic (caused by stimuli that do not normally trigger pain) or hyperalgesic (pain perception is much greater than would be expected from a normally painful stimuli). The distinction between nociceptive pain (somatic and visceral) and neuropathic pain is clinically important as different therapeutic approaches are often needed to achieve relief.

7.2.2 Approach to the Cancer Patient in Pain

One of the most significant challenges facing the clinician is to build an objective framework from which to assess and monitor the patient's subjective, or self-reported, experience of pain [20]. Without it, measuring the progression of disease and understanding the impact and efficacy of therapeutic interventions are difficult. Various interview techniques, assessment tools, technologies, and scales have been evaluated and deployed for this purpose. Particularly challenging patients include infants and children, the elderly, and those with mental incapacity or inability to communicate.

The NIH (National Institute of Health) Toolbox of Neurological and Behavioral Function that was developed to provide a set of measures derived from scholarly and expert input to measure various aspects of neurologic function recommends a self-report measure of pain intensity using a 1–10 rating scale [21]. Visual analog or verbal rating scales also have important roles to play. Regardless of what reporting scale is used, it must be impressed upon patients and their families that they must report pain and be an active partner in its management. The clinician should ask about pain frequently and, at a minimum, at every clinical encounter. Understanding and tracking the location, quality, mitigating and exacerbating factors, triggers, and temporal patterns are essential in diagnosing the etiology of, and treatment for, the symptom. Ongoing efforts to develop universal pain classification systems as a means to improve assessment and facilitate research are underway [22].

Physical examination can provide important clues to the etiology of pain, especially if it is neuropathic in origin. It is important always to take a moment and

simply observe the patient. Do they appear comfortable? Are they grimacing or furrowing their brow? What is their respiratory rate? Are they tachypneic? A finding of any of these could indicate the presence of unacknowledged pain. The lack of such finding, however, does not rule out the presence of pain especially if it is chronic in nature. An area of erythema, swelling, or tenderness to palpation can direct attention to a specific etiology and elicitation of hyper- and dys-, or anesthesia in a region can indicate a neuropathic pain problem. Even, however, if the encounter yields no useful information, physical examination is an occasion of appropriate (procedural) touch by the provider. Touch has been suggested to be helpful in communication and, hence, patient satisfaction [23].

7.2.3 Management of Cancer Pain

The World Health Organization (WHO) has, for over 25 years, promulgated a three-step pain management paradigm that has garnered near-universal acceptance as normative for pain management strategies in adults [7]. A separate two-step approach is recommended for children.

The basic WHO approach recognizes three fundamental categories of analgesics – non-opioids (aspirin, acetaminophen, paracetamol, or NSAIDs), "weak" opioids (codeine), and strong opioids (morphine, hydromorphone and others) – and three levels of pain (mild, mild-moderate, and moderate-severe). Mild pain is recommended to be treated with non-opioids, mild-moderate with "weak" opioids +/– a non-opioid, and moderate-severe with strong opioids +/– non-opioids. Adjuvant medications are recommended on an ad hoc basis, and in all cases, the WHO paradigm recommends around-the-clock dosing of analgesics with provision of breakthrough or rescue doses and adaption of regimens based upon individual needs, patient education, and administration via the oral route when possible.

While an essential strategy for pain management and advocacy for increased access to opiates in resource-limited regions of the world, this approach includes several aspects that warrant further consideration in cancer pain. These include the use of low doses of strong opiates for mild-moderate pain (elimination of step 2 on the ladder), clinical implications of long-term use of NSAIDs, validation of various routes of administration pain, addition of a fourth step that recruits surgical and other interventions for severe and intractable pain, and specific recognition of neuropathic pain requiring a different approach [24, 25].

Table 7.1 summarizes the array of approaches to treat cancer pain available to practitioners in the United States.

7.3 Opioids

Opioids are the backbone of most all strategies to control cancer pain. There are three types of opiate receptors in the central and peripheral nervous systems whose role has been well established in pain management. Originally called mu, delta, and kappa, these receptors were renamed MOP, DOP, and KOP, respectively, in 2000 by

Table 7.1 Standard ways of relieving pain

Method	Application	Effectiveness	Comments and references
Opioids	Somatic pain Neuropathic pain Mixed pain		In one underpowered randomized trial, methadone had no more effect than morphine in neuropathic pain
Adjuvant drugs Antidepressants Neuroleptics/seizure medications Steroids	Somatic pain Neuropathic pain Mixed pain		
Bone strengtheners	Bisphosphonates Denosumab	50–70 % of patients report benefit May delay bone pain more than bisphosphonates but substantially more expensive ($2500 or more versus $600)	
Radiation therapy	Bone pain Incident pain (pain on movement of bones, for which opioids are only partially effective, at the cost of oversedation) [26]. A few patients have been treated with opioid switching and "burst" ketamine at 100 mg/day [27]	70 % or more experience pain relief	
Surgery		Very little actual data May be used more for obstruction	
Nerve blocks	Celiac and other plexus blocks Local injections	In general, about a 75 % chance of success, with the ability to repeat in the future if needed	

Table 7.1 (continued)

Method	Application	Effectiveness	Comments and references
Advanced locoregional pain techniques	Spinal cord stimulation Peripheral nerve stimulation Intrathecal infusion Scrambler therapy	Over half of patients experience significant benefit Appears similar to spinal cord stimulation but with no randomized trials Randomized trial shows better pain control, less drug toxicity, and longer survival compared to conventional best pain management One randomized trial and multiple uncontrolled trials show effective relief of pain with minimal side effects	

the International Union of Pharmacology. There is a fourth receptor called the nociceptin receptor or NOP which, although has similar biochemical structures to the classic opioid receptors, does not appear to react to naloxone and, hence, is considered a non-opioid branch of the opioid receptor family [28].

Opioid analgesic drugs are classified by their strength, by the type of action they have on opiate receptors (full opioid receptor agonists, partial agonists, and mixed agonists/antagonist), and by whether they are semisynthetic (derived from the opium poppy *Papaver somniferum* extract), or fully synthesized.

All opioid agents act on central MOP receptors that, in turn, modulate pain by activating descending inhibition pathways. Many agents, morphine included, act on the other opiate and non-opiate receptors as well. The notorious side effects of opiate use (constipation, nausea, respiratory depression) are thought to also arise from agonizing these same receptors.

The National Cancer Institute (NCI) of the National Institutes of Health (NIH) publishes and frequently updates a comprehensive, peer-reviewed, evidence-based summary of information on pain management. Recommendations regarding pain management in this section are drawn from this important resource [29].

The goal of an opiate regimen is to achieve a steady state of analgesia with the fewest side effects, the greatest ease of administration, and at the lowest cost. Although the European Association of Palliative Care has suggested that there is little difference between full agonist opiates in terms of analgesia or side effects [30], many clinicians develop their own preferences and practices. In choosing among opiates, individual patient effectiveness and side effects, cost, presence of metabolites, underlying health conditions, and ease of administration are all important factors.

Opioid dosing can be highly variable from patient to patient and must be tailored to individual responses and characteristics. A patient who has never taken opiates before will achieve analgesia (and experience side effects) at a much lower dose than someone who has previously been exposed, either through legal prescriptions or illegal means.

A strategy for moderate or severe pain should commence with short-acting opiates given under close observation on an around-the-clock basis with a PRN rescue dose used in the case of breakthrough pain. Once a good balance between analgesia and side effects has been achieved, the total daily dose of short-acting agents can be converted to longer-acting formulations. Short-acting breakthrough opiates are still necessary and should always be available. In general, the short-acting breakthrough dose should be 10–20 % of the total daily dose given as needed every 1–4 h. Starting doses depend on the potency of the agent chosen. A strategy that starts with conservative dosing rapidly escalates to achieve pain control (for moderate pain daily increases by 25–50 % and higher for severe pain), and close monitoring of the patient for side effects, especially respiratory depression and level of consciousness, is recommended. There are no maximum doses for strong opiates.

It is often necessary to switch from one opiate to another or from one route of administration to another. For all opiates other than methadone, relative potencies are well described and calculations based upon them straightforward. The total daily (24 h) dose of the current medication is converted to the equivalent oral morphine amount. That amount is then converted to the equivalent of the new drug based upon the equivalency between it and oral morphine to determine a total 24-h dose of the new drug. This dose is then reduced from 25 to 50 % to ensure safety and then divided by the number of times in a 24-h period the new drug is given.

With rare exceptions, the best route of administration in a patient with a functioning GI tract and the ability to swallow without aspirating is oral. Rectal or transdermal routes are good alternatives; however, transdermal approaches are inadequate for acute or breakthrough symptoms. Opiates [31] should never be administered intramuscularly. If parenteral approaches are needed, IV and subcutaneous routes are equally effective. Because, however, the preparations of opiates used in these routes have greater bioavailability, the doses are one half or less than the oral equivalent. Some patients may benefit from intraspinal or intrathecal administration of opiates. In the largest randomized trial comparing intraspinal to regular pain management, pain was better relieved, there were fewer side effects, and patients lived 102 days longer [32].

Morphine is the best known and globally the most widely used full opioid agonist. It is available in both long- and short-acting formulations and can be administered via a number of routes. Like other full agonists, morphine will not reverse or antagonize other agonists administered simultaneously. It has become the "gold standard" also in the sense that potency of other opioids is measured against oral morphine. Controlled-release preparations typically have initial effect in 1 h, peak in 2–3 h, and last for up to 12 h.

Methadone, another agonist, is an attractive alternative because of its rapid oral and rectal absorption, lack of active metabolites, and low cost and availability in a liquid form. It has not been ruled out as a first-line agent for pain by the NIH expert panel. Difficulties with its use relate to its relatively erratic half-life, difficulty in determining equianalgesic levels with other opioids (the NIH consensus document outlines five different methods of determining initial methadone doses when switching from another opiate to methadone), and possible deleterious cardiac effects related to prolonged QT intervals. It should not be given in the presence of any other drugs that may prolong QT intervals. Consultation with a clinician expert who is experienced in the use of methadone is important, especially if this drug is chosen by an inexperienced provider. While it is commonly thought to have more N-methyl-d-aspartate (NMDA) receptor antagonist activity than morphine, and thus to be more effective in neuropathic pain, the only comparative randomized trial showed no major differences [33].

Short-acting preparations are appropriate for acute pain and for breakthrough or rescue dosing. Their effect usually begins within 30 min of administration and lasts for 4 h.

Fentanyl, because it can be administered transdermally, as a sublingual spray, or as a lozenge, pill, a film that dissolves orally, nasal spray, IM, or IV, can be especially useful in certain situations. A fentanyl patch is, however, not appropriate for acute pain as it takes about 12 h for the effect to start, another 12–24 h for it to peak, and generally lasts for 72 h. Fentanyl is also less absorbed in cachectic patients and required twice as high a dose as normal weight patients in one study [34]. Other full agonists that can be used in cancer pain include hydromorphone, codeine, oxycodone, oxymorphone, hydrocodone, and levorphanol.

Meperidine, which has a neurotoxic metabolite that accumulates over time, is a poor choice, especially with renal failure. Partial and mixed agonist–antagonist drugs like pentazocine, butorphanol tartrate, dezoine, and nalbuphine hydrochloride are also unsuitable because of their inherent maximum ceiling on analgesia effect. Preparations that combine an opioid with a non-opioid agent are limited by toxicities associated with the non-opioid component.

Because opiates retard gut peristalsis, stool in patients becomes dehydrated, and, unless obstruction or diarrhea is present, the patient experiences constipation. All patients taking opiates, therefore, should be given prophylaxis against constipation using, at a minimum, stool softeners. Most will also require mild osmotic agents, polyethelene glycol, and bulk-forming agents or cathartic laxatives such as senna or bisacodyl. It must be remembered that osmotic and bulk agents require oral

hydration to be effective. Sennosides are the mainstay at most hospices because of effectiveness, tolerability, low cost, and there is no added effect of adding docusate to senna [35].

Nausea and vomiting often accompany use of opiates. The mechanisms responsible are stimulation of the chemoreceptor trigger zone – a dopamine-mediated event – reduced gastrointestinal motility, and, rarely, increased vestibular irritation. Metoclopramide, which can be given via oral and parenteral routes, and domperidone, which is only available orally, both improve gastrointestinal motility and have antidopaminergic effects. Consequently, these two drugs are often a first-line choice. In the United States, domperidone is not available except by special dispensation, so it is rarely used. Histamine [36]-blocking agents impact on the vomiting center and vestibular system and have their best utility when vestibular involvement is present. Haloperidol and phenothiazines are also useful, especially when motility-enhancing agents are contraindicated. Anticholinergic side effects often limit the use of chlorpromazine and anticholinergic drugs such as hyoscine hydrobromide.

Neurocognitive side effects of opioid use are not fully understood but appear, in part, to be related to opioid metabolites. Toxicities can include hallucinations, myoclonus, cognition deficits, delirium, allodynia, and hyperalgesia. In the case of a patient who demonstrates the latter symptom after starting or increasing an opiate, toxicity should be considered. Patients with renal failure or advanced disease are especially prone to neurocognitive side effects. Because morphine and hydromorphone have different active metabolites and methadone has none, clinical strategies to switch between these agents have been used to minimize neurocognitive dysfunction. A patient with cancer, especially in an advanced state, who presents with nonfocal neurological symptoms of delirium or other global dysfunction, should be ruled out for side effects of other medications, dehydration, constipation, hypercalcemia, and/or sepsis.

7.4 Adjuvants (Coanalgesics)

These pharmacotherapies are used most often in conjunction with opiates to treat nociceptive pain. In some instances of neuropathic pain, however, select adjuvants can rightly be used as effective first-line therapy [37].

Nonsteroidal anti-inflammatory can serve an adjuvant role in management of cancer pain. A meta-analysis showed that single doses had a rough equivalent to 5–10 mg of intramuscular morphine. The analysis noted, however, a lack of evidence for a role in malignant bone pain. Side effects (GI bleeding, dizziness, and drowsiness) increased with dosage and showed no ceiling effect [38].

Tricyclic antidepressants (TCAs) that retard both norepinephrine and serotonin reuptake act by augmenting modulation of pain impulses at the ganglion. They make an additional contribution to pain management by treating depression itself – a state known to heighten pain perception [39]. TCA's anticholinergic effects often limit their dosage and, hence, impact. The clinical utility of newer antidepressant

agent classes, selective serotonin reuptake inhibitors, and selective serotonin–norepinephrine inhibitors, in pain management, is under investigation.

Gabapentinoids (gabapentin and pregabalin) are antiepileptic drugs that inhibit calcium release at gated calcium channels in pain pathways, depress hyperexcitability, and thus depress neurotransmission. They can be effective agents in management of neuropathic pain, work synergistically with opioids as adjuvants, and are generally well tolerated although somnolence and dizziness can limit dosage [40]. Other anticonvulsants to be considered include carbamazepine, valproate clonazepam, and lamotrigine.

Local anesthetics (mexiletine and lidocaine patch), psychostimulants (dextroamphetamine and methylphenidate), baclofen, calcitonin, clonidine, octreotide, and bisphosphonates have all been used as adjuvants in cancer pain management with varying levels of success. These are reviewed in the NCI Physician Data Query (PDQ) publication.

Corticosteroids have been widely used in managing patients with cancer pain. Aside, however, from a well-established role in managing certain types of disease (e.g., mass effect of CNS tumors and pain ensuing from increased intracranial pressure), the evidence supporting use of corticosteroids as analgesic agents is not strong and more research is needed if a firm role for them is to be adopted [41]. In one well-designed trial, dexamethasone added to metoclopramide was no better than placebo in reducing nausea [42]. Dexamethasone 4 mg bid has the added effect of improving quality of life and reducing fatigue, compared with placebo, near the end of life [43].

7.5 Important and Common Clinical Situations

Tumor invasion of bony structures causes significant pain and morbidity. The clinician should be especially vigilant to identify bone pain and to rule out or address impending pathological fractures (especially if there is spinal disease and a potential for spinal cord compression). In addition to standard pain management approaches as described above, any bony involvement should prompt consideration of bisphosphonates, which are known to prevent skeletal-related events and pain in advanced breast cancer, multiple myeloma, prostate cancer, and lung cancer [44]. These drugs are also beneficial for the hypercalcemia that often accompanies advanced metastatic disease. Calcitonin has also been used to treat pain arising from cancer involving bone. A recent Cochrane review did not, however, find sufficient evidence to endorse this approach [45].

External beam radiotherapy (EBRT) is a well-documented means of addressing pain arising from bone cancer and strengthening bones damaged by tumors. A number of studies have demonstrated that single fraction therapy is equally efficacious and more cost-effective than multiple fraction therapy [46]. Radioactive particle therapy that seeks bone by binding to phosphates can relieve pain and reduce skeletal events [47], and one isotope actually prolonged survival in patients with metastatic prostate cancer [48].

Cancer-related bowel obstruction can result in significant suffering with severe symptoms and pain. In addition to standard analgesic antisecretory drugs, antiemetics and even surgical interventions (venting gastrostomy, stent, diverting ostomies, and more) are often necessary to achieve comfort. Nasogastric tubes are frequently a cause of pain themselves and should only be used on a temporary basis to relieve symptoms [49].

7.6 Looking to the Future

Advances in cancer pain management will come from a better understanding of the pathophysiology of pain, discovery of novel medications and techniques to treat pain, and smarter educational and public policies directed at promulgating pain management techniques into healthcare systems.

There are other novel ways of relieving pain that do not rely on drugs. Spinal cord stimulation, in which an electrode is positioned on the dorsal column of the spinal cord itself, can dramatically reduce pain of all types but must be performed by an experienced group using appropriate safety measures [50]. Similar techniques used for peripheral nerve stimulation have evolved over the past decade often with dramatic success, but there are no randomized comparison trials [51]. A noninvasive type of peripheral nerve stimulation using the body's own C-fibers to conduct electrical impulses labeled as "non-pain" information is similarly promising with apparent dramatic effectiveness in cancer abdominal pain [52], cancer pain [53], chemotherapy-induced neuropathy [54], and other types of neuropathic pain; [55] randomized placebo controlled trials are ongoing.

The new and exciting technologies are not restricted to electrical stimulation. High-intensity "cold" light therapy, or photon stimulation with light-emitting diodes (LEDs), can improve some diabetic pain qualities and improve mood and quality of life compared with placebo light therapy – with just four treatments [56]. Other approaches include augmentation of microglial cells with stem cell transplantation [57], novel sodium–calcium channel blockers at the dorsal root ganglion, nerve growth factor augmentation, and a variety of other novel approaches [58].

Well-designed research ensures the use of *current* technologies by understanding the barriers at the patient, family, provider, payer, and systems levels [59]. Patient involvement and activation methods such as PRO-SELF, a nurse-coaching method, worked well in the United States [60] and Germany [61] but not quite as well in Norway [62]. Having a palliative care team involved alongside the usual oncology care has shown reduced symptoms in most of the randomized clinical trials [63] and is now standard practice [64].

The World Health Organization's executive board adopted a resolution entitled "Strengthening of palliative care as a component of integrated treatment within the continuum of care" on January 23, 2014 [65]. This was a watershed moment for legitimizing palliative care globally and, hence, set the groundwork for improved

cancer pain management around the world. With the imprimatur of the WHO behind it, the effort to build and integrate palliative care into health systems, rather than to isolate it as an "add-on" or optional set of services, gained new strength and visibility.

This advance did not occur in isolation. It was, rather, the culmination of a long and difficult struggle by many individuals and organizations dedicated to improving pain management for people living with serious illness including, but not limited to, cancer. Reaching back to the earliest years of the palliative care movement at St. Christopher's Hospice in London, through the formation of hospice and palliative care institutions and educational programs in Europe, North America and other regions by visionary leaders, to an international coalescence embodied in entities like the United State's National Hospice and Palliative Care Organization (NHPCO), the University of Wisconsin's Pain and Policy Studies Group, the Worldwide Palliative Care Alliance, the American Academy of Hospice and Palliative Medicine, the Diana Princess of Wales Fund, the African Palliative Care Association, Help the Hospices (UK), the President's Emergency Plan for AIDS Relief, and many others, a critical mass of political will and compassion was marshaled and deployed to good effect on the global stage.

This achievement is best viewed as an opportunity for renewed efforts to improve the management of pain with cancer patients by expanding palliative care. In the United States, a survey of academic medical school deans in 2004 found that although 84 % viewed end-of-life care as being "very important," difficulties in providing appropriate education (lack of time in the curriculum, lack of faculty expertise, and absence of a faculty leader) made the issue difficult to address [66].

One of the most important ways that leadership and expertise are fostered is through the creation of focused training programs and specialty certifications. In the United States, board certifications have been established in palliative care for medicine, nursing, social work, and chaplaincy. Since 2012, certification is only available to physicians who have active board membership in an approved field (pediatrics, medicine, etc.) and who have completed an additional year of approved fellowship training in palliative medicine.

This growth in education and professional stature has been paralleled by a significant growth in hospital-based palliative care programs. The Center to Advance Palliative Care has determined that, among US hospitals with 50 or more beds, the number of palliative care programs increased 125 % between 2000 and 2008 [67]. Additionally, the Joint Commission has recently begun a process to recognize hospital inpatient programs that demonstrate exceptional patient- and family-centered palliative care.

These trends are likely to strengthen as the impact of palliative care on healthcare costs is better understood. Rather than being an additional cost center for health systems, recent research points to significant cost savings associated with refocusing goals of care (typically to pain management, comfort measures, etc.) and thus avoiding high cost interventions that do not advance or support them [68, 69].

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